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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,201	03/08/2006	Carmen Barske	PN/4-32761A	1795

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,201	BARSKE ET AL.	
	Examiner	Art Unit	
	SANDRA WEGERT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *10-16 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Information Disclosure Statement, sent 9 June 2005, has been entered into the record. Applicant's election of Invention I (claims 1-9 and 17) with the species of NOGO antigen of SEQ ID NO: 6, in the Paper of 15 July 2008, is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 10-16 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim.

The Restriction requirement is deemed proper and is therefore made FINAL.

Claims 1-9 and 17 are under examination in the Instant Application.

Informalities

Specification

The disclosure is objected to because of the following informalities:

URL's

The disclosure is objected to because it contains browser-executable code. This occurs, for example, on page 2, at the end of the second paragraph, for example. All URL's should be

removed from the Specification. Applicant may refer to web sites by non-executable name only. See MPEP § 608.01 (p).

Appropriate correction is required.

Claim Rejections/Objections

Claim Rejections - 35 USC § 112, second paragraph, indefiniteness.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.**

Claims 2-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite or encompass "hypervariable regions" and then list CDR1, CDR2, CDR3, etc, as the regions themselves. In fact, the hypervariable *region* of an antibody light chain or heavy chain is made up of three segments: CDR1, CDR2, CDR3. Thus, it cannot be determined if applicants are referring to the hypervariable region as a whole, or to the parts of the region. Referring to the hypervariable region and then to its separate components would be remedial, as would removing references to a hypervariable region (since the CDR's are known to comprise the hypervariable region).

Claims 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the characteristics of a molecule that binds various Nogo

epitopes, and also recite "direct equivalents thereof." It is not known if this phrase refers to functional equivalents or structural equivalents, or something else altogether. Defining what is meant by both "direct" and "equivalents" would be remedial, as would removing the phrase.

35 U.S.C. 101, Product of Nature

The following is a quotation of 35 U.S.C. 101:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.**

Claim 1 is rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claim reads on a product of nature in that the claimed antibody is not "isolated." For example, the claims encompass polyclonal sera that has not been removed from the human or animal. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty,* 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified". See MPEP 2105.

Claim Rejections- 35 USC § 102

The following are quotations of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

Claim 1 and 17 are rejected under 35 U.S.C. 102(b) as being unpatentable over Chen, et al, (2000, Nature, 403: 434-439). Chen, et al disclose an antibody that binds human NogoA_623-640 (SEQ ID NO: 6) with a dissociation constant < 1000nM. The paper discloses an antibody, *AS472*, that was generated specifically against the short segment of NogoA from residues 623-640 (see Figure 1, part a, the boxed portion in the middle of the sequence). The authors stated that the affinity of their antibody was in a range close to that of Spillman, et al, (1998, J Biol Chem, Vol. 273, Issue 30, 19283-19293), which was about 2 nM (see first paragraph of the Discussion). This is a typical affinity for an antibody, and is well within the range required by the claim of <1000nM. The authors also applied the antibody "in situ" to spinal cord slices (Figure 2), meaning that it was applied in a pharmaceutically-acceptable solution (such as water or saline). Thus, this reference meets the limitations of claims 1 and 17 of a molecule that binds NogoA_623-640 with a dissociation constant < 1000nM and applied as a composition in a pharmaceutically acceptable carrier or diluent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen, et al, (2000, Nature, 403: 434-439) and further in view of Bendig, et al, (1996), U.S. Patent No. 5,558,864.

Claim 8 is drawn to the chimerized or humanized antibody of claim 1.

The teachings of Chen et al. are described above. Chen et al does not recite methods used to chimerize or humanize an antibody.

Bendig, et al, teach antibodies generated against Epidermal Growth factor receptor, as well as techniques and products for humanizing mouse antibodies by substituting the CDR's of the mouse antibodies with the corresponding human CDR's (shown throughout the Disclosure, but see specifically Columns 5 and 6). They also confirmed that the modified antibodies bound human EGFR approximately as well as the original mouse antibodies (see the competition binding curves of Figure 7).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to humanize or chimerize an antibody made in a non-human animal for use as a binding agent to bind human NOGO. There is a finite number of CDR sequences to choose from that would result in a humanized antibody, and a reasonable expectation of success for producing such an antibody. Chen et al has taught that antibodies can be generated in mice that bind with high affinity to NOGOa_623-640, and Bendig, et al teach that mouse antibodies can be

humanized with a reasonable chance of success. In addition, the skilled artisan would be motivated to humanize a non-human antibody because Bendig, et al, teach that non-humanized antibodies are potently immunogenic when administered to humans (column 2). Keep in mind that the suggestion of humanizing non-human antibodies does not have be explicit and "may be found in any number of sources, including common knowledge, the prior art as a whole or the nature of the problem itself" (See Pfizer, Inc. v. Apotex, Inc., Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007); KSR International Co. v. Teleflex Inc., 550 U.S. —, 82 USPQ2d 1385 (2007) and MPEP § 2141, part III.)

Claim Rejections - 35 USC § 112, first paragraph – scope of enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 2-7 and 9 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for an antibody that binds NOGO, comprised of SEQ ID NO: 8, 9, 10 in the heavy chain and SEQ ID NO: 11, 12 and 13 in the light chain, does not enable variants of the CDR sequences that are at least 50% homologous to SEQ ID NO: 8, 9, 10 and SEQ ID NO: 11, 12, and 13, in the heavy and light chains, respectively, or that are *direct equivalents thereof,* or that *comprise polypeptide sequences* as shown in SEQ ID NO: 2 and 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

The specification is not enabling for the full scope of the claimed peptides compromising the CDR's, wherein the amino acid sequences are 50% identical or *direct equivalents* to the disclosed CDR sequences, with the assurance that claimed proteins that are functionally equivalent to the disclosed CDR sequences can be made without undue experimentation and with the assurance that together they would have the desired property of binding NOGO with high affinity and specificity. There are no examples of what specific antibodies fall within the range of those that would be 50% identical. Neither is it clear if this percent identity need be over a contiguous region or a specific portion of the polypeptide. However, it is known from the antibody art that the structural characteristics and shape of the binding regions of an antibody are highly variable, even in the case of multiple polyclonal antibodies generated against the same antigen. It would stand to reason then that the secondary structure that results in such diverse tertiary and quaternary structures would also vary widely and in unexpected ways (Macallum, et al, J. Mol. Biol. (1996) 262: 732–745, see Table 1, the Interface area and Topography of antibodies generated against Hen egg lysozyme).

In addition, the specification does not enable a "binding molecule comprising polypeptide sequences shown in SEQ ID NO: 2 and SEQ ID NO: 3," as recited in claim 9. The claim as written encompasses combinations of the disclosed polypeptide sequences as well as fragments, none of which have been synthesized or verified to be functional NOGO binding molecules.

In summary, the specification does not provide a description of a repeatable process of producing, nor of working examples of making antibodies directed against Nogo whose amino acid sequences deviate from the disclosed series of sequences (SEQ ID NO: 8, 9, 10 and 11, 12,

13) by as much as 50%. For this reason, undue experimentation would be required to determine a structure-function relationship for each possible polypeptide encompassed by the claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Due to the large quantity of experimentation necessary to determine an activity or property of the claimed antibodies such that it can be determined how to use the claimed antibodies and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the lack of direction/guidance presented in the literature, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims -- undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, first paragraph – Written Description.

Claims 2-7 and 9 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims are directed to an antibody that binds NOGO, comprised of SEQ ID NO: 8, 9, 10 in the heavy chain and SEQ ID NO: 11, 12 and 13 in the light chain, and having sequences that are at least *50% homologous* to SEQ ID NO: 8, 9, 10 and SEQ ID NO: 11, 12, and 13, or *direct equivalents* [of 50% homologous] in the heavy and light chains, respectively, or that *comprise polypeptide sequences* as shown in SEQ ID NO: 2 and 3. Keep in mind that applicants were not in possession of a "binding molecule comprising polypeptide sequences shown in SEQ ID NO: 2 and SEQ ID NO: 3," as recited in claim 9. The claim as written encompasses a large number of combinations of the disclosed polypeptide sequences, as well as fragments, none of which have been synthesized.

The specification teaches an antibody comprising SEQ ID NO: 8, 9, 10 and SEQ ID NO: 11, 12, and 13. However, the specification does not teach functional or structural characteristics of all claimed antibody polypeptides. The description of one anti-Nogo antibody is not adequate written description of an entire genus of functionally equivalent peptide antibodies.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the polypeptides that must be conserved. Accordingly, in the absence of

sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the anti-Nogo antibody disclosed, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound *itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483 (BPAI 1993). In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated antibodies comprising SEQ ID NO: 8, 9, 10 and SEQ ID NO: 11, 12, and 13, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written

description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion: Claims 1-9 and 17 are rejected for the reasons recited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) 272-0939.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

/SLW/
22 September 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646